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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,925	07/30/2000	ELIAS GEORGES	641050.90013	9902

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,925	GEORGES ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6,7,15-27,30-33,37 and 37-42* is/are pending in the application.

4a) Of the above claim(s) *6,7,24-27,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *15-23,32,33 and 37-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's response to the Office Action mailed January 23, 2003 on July 29, 2003 is acknowledged. The amendments to the specification filed on July 25, 2003 has been entered.

2. Claims 1-5, 8-14, 16, 19, 28-29, 34-35, and 38 have been canceled. Claims 41-42 have been added. Claims 15, 17, 20, 37, 39 and 40 have been amended. Claims 6-7, 15-27, 30-33, 37 and 37-42 are pending. Claims 15-23, 32-33 and 37-42 are under examination.

3. The following grounds of rejection are or remain applicable:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 17-18, 20-23, 39 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For clarity claims 20 and 39 need to be amended to remove the recitation of "directly" as claim 15 has been amended to remove this language, as it is recited that the claimed compound is "directly" affecting Annexin-based MDR, however, it is not apparent whether or not a method in which cell membrane integrity is compromised would or would not be considered direct; or, does direct mean one to one physicochemical interaction of the candidate drug with the biological agent effecting MDR? How does the claim distinguish directly from

indirectly? It is not readily apparent where in the specification that "directly" is defined. Thus the claims remain indefinite. The dependent claims are included in this rejection.

Claim 20 is indefinite because the mere recitation of the acronym MDR is not sufficient to convey what applicant intends the invention to be and for clarity all independent claim should recite the spelled out meaning of the acronym (see also claims 32 and 39 for example).

Claims 17 and 18 remain indefinite with regard to the Markush listing. The claims recite "a nucleic acid molecule encoding an Annexin variant, **or part thereof,** an Annexin antisense molecule, a **mutant Annexin**, an antibody to Annexin and a peptide". Note that the Markush listing is confusing and inconsistent (with regard to administration of a protein as opposed to administration of a polynucleotide), double inclusion (with regard to mutant annexin, variant or part thereof which is included in the broad term "mutant annexin"). See also claims 41-42.

Claim 32 and all other claims with this language are indefinite because the claim recites "increase in the expression of an annexin protein, whereby said increased expression is capable of conferring MDR", as applicant on pages 11-12 of the response states that over-expression of a gene in a cell displaying a specific phenotype is not reliable proof that the gene causes this phenotype. Thus, it appears applicant statement contradicts the invention as claimed.

Claim Rejections - 35 U.S.C. §103

The following is a quotation of 35 U.S.C. 103 (a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

6. Claims 15, 16, 17, 19-20 and 37-40 32 and 33 are rejected under 35 U.S.C. 103(a) as obvious over Wang et al. (Biochemical and Biophysical Research Communications, vol. 236, pages 483-488, 1997) based on the disclosure which states that P-40 is Annexin I and that the invention relates to the identification of Annexins (I-XI, also referred to herein as P-40 and P-40 homologs (see page 4 of the specification).

Wang disclose a method comprising the binding of IMP96 to P-40 in MCF-7/Adr cells (see Figure 1) and demonstrates that P-40 (Annexin I) confers resistance to Taxol and Adriamycin (see Table 1 and discussion on page 486). Wang further discloses that the over expression of P-40 in paclitaxel or cis-platinum selected cell lines, in the absence of a detectable level of P-gp or MRP supports the notion that P-40 alone may confer resistance to cytotoxic drugs (see page 486). Wang also disclose that P-40 could modulate an MDR phenotype

indirectly, by stating that P-40 may be a component of the apoptosis signaling pathway. Moreover, Wang discloses that changes in the levels or functions of proteins involved in the signaling of apoptosis can confer an MDR phenotype on tumor cells (see page 487). Wang also disclose a method that identifies a protein that mediates drug resistance to anticancer drugs. Wang further discloses a method that was used to isolate a monoclonal antibody (IPM96) which recognized a protein (P-40) co-expressed with P-glycoprotein in several resistant cell lines. Additionally, Wang discloses that over expression of P-40 (protein which is Annexin) in multidrug resistant cells may be important in the expression of the drug resistance phenotype (see pages 483-485).

The Wang reference identifies a compound (P-40) that affects Annexin-based MDR in a cell in the presence of a drug (Adriamycin and Taxol) and assessed the effect of said compound as claimed in the present application. Further, Wang discloses a method that utilizes an antibody to Annexin and a compound that modulates Annexin based MDR in a cell as the present application discloses that P-40 and Annexin are equivalent. Although Wang does not teach a direct correlation as recited in claim 20 for example, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole because Wang teaches that there is an indirect correlation and that P-40 is important in the expression of drug resistance phenotype, thus provides a suggestion for a direct correlation. Furthermore, it is not apparent whether or not a method in which cell membrane integrity is compromised would or would not be considered to be "direct". Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

7. Applicant's arguments filed on July 29, 2003 have been fully considered but were not persuasive. Applicant presented an argument that the reference of record does not anticipate the

claimed invention. Note that the rejection has been changed to an obvious type rejection. Applicant amended claim 15 to remove the language "directly which remains in several other independent claims and contends that directly means "Annexin contributes to MDR" (see page 8 of the response) which is the suggestion made in the reference of record and the requirement under 35 U.S.C. 103(a), a mere teaching or suggestion. Applicant's arguments on pages 10-12 are noted, however are not fully persuasive because, the reference on page 483 discloses that " [T]aken together, the over expression of P-40 in multidrug resistant cells have been previously determined and therefore could be important in the expression of the drug resistance phenotype. Transfection studies using cDNAs encoding *mdr1* and *mrp1* genes have clearly demonstrated that P-gp or MRP is sufficient to confer an MDR phenotype onto otherwise drug sensitive cells". Applicant then contends that the Wang reference does not teach this direct correlation. Thus, the Wang reference remains relevant.

Regarding the rejections under 35 U.S.C. 112, second paragraph, applicant amended claim 15 with regard to the recitation of the language "directly", however, did not amend claims 20 and 39 although the rejection "stated that "claim 15 and all claims reciting this language are indefinite/unclear. Thus, the rejection remains. Applicant responds to the rejection over claims 17 and 18 by stating that the claims were reformulated, however, the double inclusion problem still remains for the reasons stated above (i.e., a variant or part thereof). Note the rejection remains over claim 32 and other claims with this language although applicant's statements in the response have been considered. It is suggested that applicant amend the claim to recite "increase in the expression of an annexin protein, whereby said increased expression [is capable of conferring] confers MDR", as the present language appears to contradict applicant's statements on the record. For these reasons and the reasons stated above, the rejections remain.

Applicant's response pointed out that newly submitted claims 32 and 33 were not examined. Based on this inadvertent error, an examination of these two claims appears in this office action.

Conclusion

8. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Hope A. Robinson whose telephone number is (703) 308-6231. The Examiner can normally be reached on Monday and Wednesday- Friday from 9:00 A.M. to 6:30 P.M. (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Christopher S.F. Low, can be reached at (703) 308-2932.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-2742. Please affix the Examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Hope A. Robinson, MS

Patent Examiner